October 24, 1996

On March 21, 1995, the Food and Drug Administration (FDA) held a public workshop entitled "Positron Emission Tomography (PET) Regulatory Workshop." During the course of the workshop, many members of the audience asked questions about a variety of issues related to the regulation of PET drug products.

In an effort to address these questions, staff members in the Offices of Generic Drugs, Compliance, and Review Management in the Center for Drug Evaluation and Research have developed answers (see attached).

The FDA understands that questions about the regulation of PET products will continue. Therefore, the Agency is undertaking additional efforts to facilitate the dissemination of information on PET drug products to industry and the public. Planned activities include a second public workshop in early 1997, and several guidance documents.

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**October 24, 1996**

**PET Questions and Answers from March 21, 1995 Workshop**

*Q1: In your transition plans, how can you ensure that this will not be disruptive to the delivery of health care in PET centers? How will financial devastation for the practitioners and other individuals and hospitals that have made these investments in these clinical care facilities be avoided?*

A: During the implementation period, we did not take regulatory action against any PET facility and we do not expect to take action against any PET facility that demonstrates a good faith effort to comply with FDA regulations by developing a well-designed written plan or procedure with reasonable and defined time frames.

*Q2: Will the FDA waive the user fees for all PET facilities?*

A: Many new drug applications from PET facilities will qualify for the small business exception or other waiver under the Prescription Drug User Fee Act (21 U.S.C. 379h(b)(2) or 379h(d)). ANDAs are not assessed user fees under current law. For information on how to apply for the small business exception or a waiver see Interim Guidance Document for Waivers and Reductions in User Fees, July 16, 1993, and Supplement, February 1, 1995 (a copy of this document can be obtained from the Industry Liaison Office, Office of External Affairs, by calling 301-827-3430).

*Q3: Within 18 months, you want every PET facility to file at least an IND, NDA, or an ANDA for every tracer that they are using. Are you looking for an IND, NDA, or an ANDA from each facility for each use of FDG?*

A: More than one clinical indication or use can be studied under a single IND application for a single drug. One NDA or ANDA may be approved for multiple manufacturing sites, as long as it contains information on each manufacturing site. Several separate institutions or PET facilities may wish to consider the submission of a single application that could cover multiple manufacturing sites.

*Q4: How are you going to regulate what is currently being used in clinical practice?*

A: PET facilities, like other drug manufacturers, are required to comply with the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). FDA has published guidance and policy statements interpreting FDA regulations to facilitate this process. Furthermore, FDA staff are ready to help any applicant in meeting the legal requirements. At a minimum, the FDA would like to see a good faith effort from the nuclear medicine and PET communities to comply within a reasonable and defined time frame according to a well-designed written plan or procedure. If the FDA determines

that a good faith effort is being made, the FDA does not intend to prevent the use in clinical practice unless a safety problem is identified.

*Q5: Most of the PET radioligands that we use have specific activities in the range of 1 curie/micromole. There really aren't very many low molecular weight compounds that would cause a pharmacological effect, let alone a toxicological effect in a human if given in a dose of 5 micrograms. Could FDA dispense with the requirement to provide toxicological information for PET drugs that don't have pharmacologic activity? Could limits (such as a specific activity of 1 curie/micromole) be set by which toxicological information could be eliminated?*

A: It would be difficult to establish a dose limit. A ligand could be highly selective and highly specific and go to receptors in a patient who already may be compromised with that receptor subtype. Agonists, and perhaps some antagonists, may have clinical effects at nanomole levels. Too many variables would have to be evaluated for each drug to set a standard dose for which no toxicological information would be needed.

*Q6: A pharmacological/toxicological waiver was granted for the one approved NDA for F-18 FDG. A literature survey was collected and circulated within the PET community. Is this an acceptable way to proceed until FDA provides additional guidance on this issue?*

A: Requirements could be waived for pre-clinical pharmacological/toxicological animal testing for other PET products based on the appropriate literature. For information on specific requirements for particular products, contact the Division of Medical Imaging and Radiopharmaceutical Drug Products in the FDA, Center for Drug Evaluation and Research.

*Q7: (a) If there is a successful ongoing IND, could it be used to support other new INDs for the same drug? (b) Would other clinical trials support a new IND for the same drug? (c) Would it be possible to reference another IND if authorization to reference is provided? (d) Could that alleviate the need to provide pharmacological/toxicological information in the second IND?*

A: (a) Yes, if it can be shown that the final drug products are equivalent, and if the sponsor obtains authorization to reference the data in the original IND.

(b) Yes, if it can be shown that the final drug products are equivalent, and if the sponsor obtains authorization to reference the data in the original IND.

(c) Yes.

(d) Yes, if the original IND contains adequate pharmacological/toxicological

information that is relevant to the second IND, the two drug products are equivalent, and the sponsor of the second IND obtains authorization to reference the data in the original IND.

*Q8: Elaborate briefly on how GLPs might impact on a hospital-based or institutionally-based laboratory that wanted to do some animal pharmacology/ toxicology studies.*

A: The Good Laboratory Practice regulations (21 CFR Part 58) apply the principles of quality assurance to toxicity (safety) testing. To ensure the quality and integrity of data submitted in safety studies performed as part of an IND or NDA, FDA requires compliance with the GLP regulations.

Some laboratories may want to conduct animal pharmacology studies. However, not all animal pharmacology studies are required to be performed according to the GLP regulations. Therefore, the effects of the GLP regulations will vary from facility to facility. Some laboratory facilities may already be in compliance; others may not. Furthermore, the GLP regulations allow IND and NDA sponsors to use consulting laboratories, contractors, or grantees to perform analyses or other services provided their work is done under the GLP regulations.

*Q9: Most of the new PET compounds being developed are actually based on other compounds that are already used in patients. The difference is replacing a hydrogen atom by a carbon atom. Do we have to go through all these pharmacological procedures that have already been validated and for which literature is available?*

A: If an atom on the molecule is changed, the possibility of a change in the toxicologic or pharmacologic profile of the drug exists. Even the distribution of the molecule could change. Because of this, data should be submitted for the changed molecule. If sufficient literature is available for the analog drug, new pre-clinical studies may not be necessary.

*Q10: When making a compound with a specific radioisotope, and the pharmacologic and toxicologic profiles are known, do you have to repeat the pharmacological and toxicological studies if only the radioisotope is changed?*

A: No. If sufficient data have been collected and submitted to the Agency for one chemical molecule, we generally assume that changing the radioisotope (e.g., 127 I to 131 I) would not change the pharmacologic and toxicologic profile. In contrast, changing H to 18 F would most likely affect the biologic profile.

*Q11: There is one approved NDA for F-18 FDG. How will it be determined that other F-18 FDG products are the same as the approved product?*

A: In reference to ANDAs, the regulations state that the generic product must be the same as the innovator product as follows:

- active ingredient
- dosage form
- route of administration
- strength

The regulations [21 CFR 314.94(a)(iii)] also require injectable products to contain the same inactive ingredients in the same concentration as the innovator. However, a parenteral product may differ in preservatives, buffers, or antioxidants as long as the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the drug product. Examples of the type of information that would describe "safety" are journal articles or reference to other approved parenteral products that contain the inactive ingredient. It should be noted that the concentrations for preservatives, buffers, or antioxidants in generic products cannot exceed the amount previously approved in a parenteral drug product.

Studies to show bioequivalence of F-18 FDG will not be required as long as the generic product uses the same inactive ingredients in the same concentrations as the innovator. Again, certain changes in preservatives, buffers, or antioxidants as described above may be permitted when seeking a waiver from the requirement to conduct a bioequivalence study. Any differences in formulation will be evaluated on a case-by-case basis to determine if a waiver of bioequivalence studies is acceptable.

*Q12: There is good literature and scientific validation for some of the PET drugs. Can this data be used as a comparator?*

A: Data from published literature that has been interpreted and analyzed properly may be adequate to support an application. It will depend ultimately on the strength of the data and its relevance to the application it is being used to support.

*Q13: Can an application consist of one prospective and one retrospective study to support an indication?*

A: Assuming they were done correctly, it would be acceptable to have both prospective and retrospective data. Although the results of two adequate and well-controlled studies are the standard submission, it is not necessary to complete two prospective clinical trials when existing data provide the information that is needed in a clinical trial. If existing data are used to support an application, the data should simulate the two trial design. However, the applicant should discuss the trials with the Agency prior to submission and the data would have to be evaluated before the application

could be approved.

*Q14: Could the authors of published literature be contacted to supplement the published data with specific information that may be needed to support the approval of an application?*

A: Yes.

*Q15: Who is responsible if CGMP violations are found?*

A: The individual or individuals who have the authority and responsibility for the operation(s) of drug manufacturing and distribution are responsible for compliance with FDA regulations.

*Q16: From a regulatory perspective, if the holder of an approved NDA would supplement the NDA with another manufacturing site, who is responsible for the adverse event reporting for the NDA?*

A: The NDA holder is responsible for submitting adverse reaction reports to the FDA.

*Q17: Regarding the Federal Register notice for the proposed CGMP rule, we would have to double the number of staff people to meet the draft CGMP guideline. The estimated times required to complete the paperwork for annual reports have been grossly underestimated. How are small centers expected to meet the requirements? Will each NDA require an annual report?*

A: Each ANDA/NDA will require an annual report, but annual reports vary in size. The reporting requirements are found in 21 CFR 314.80 and 314.81. If several sites are covered by the ANDA/NDA, only one cumulative report is needed.

*Q18: What are the differences between exceptions, alternatives, exemptions, and waivers?*

A: In the CGMP context, the FDA has indicated in the draft CGMP guideline that it will entertain requests for exceptions and alternatives to the CGMP regulations. An exception would be requested when the regulation cannot be meaningfully applied to PET drug manufacturing. An alternative would be requested when a different method could be substituted for the accepted method. The terms "exemption" and "waiver" do not apply in this context.

*Q19: Is there a different set of regulations for small-scale versus large-scale manufacturing?*

A: No. Although the regulations (21 CFR Parts 210 and 211) do not distinguish between small-scale and large-scale manufacturing, certain site-specific activities and practices may qualify for an exception or alternative.

*Q20: Does the FDA intend to publish which waivers, exceptions, exemptions, and alternatives have been granted?*

A: Periodically, the Agency will publicly disseminate information on the types of exceptions and alternatives it has granted.

*Q21: When preparing ANDAs, if we know that one applicant has obtained an exception, can we assume we will also receive the exception?*

A: Exceptions and alternatives must be requested and justified on a case-by-case basis. The FDA will make every possible effort to treat like situations alike.

*Q22: Could exceptions be classified according to what cyclotron system you are using and similar black box setups?*

A: Current good manufacturing practices apply to manufacturing processes and not to individual pieces of equipment. Similarly, exceptions and alternatives to the CGMPs will likely apply to manufacturing processes. It is hard to predict what logical grouping could be made until we see the actual applications. It is conceivable, but we will have to wait and see what mechanism is possible.

For example, sampling and testing of in-process materials and drug products (21 CFR 211.170) could create problems due to radiation safety concerns. If the radiation safety risks outweigh the quality control benefits, an exception could be proposed to this part of the CGMP regulations. However, another quality control measure that reduced the potential risks to product quality, such as parameter checks of critical processing steps, would have to be present. Once established, this type of quality control measure could potentially fulfill the intent of this part of the CGMP regulations.

*Q23: Many PET facilities are synthesizing drugs for both research and clinical use. Is it possible to carry on an active basic research program in a facility that is also producing CGMP drugs in the same facility?*

A: Yes.

*Q24: At what point during the process should the request for an exemption to CGMP regulations be requested?*

A: The request for an exception or alternative can be sent to the FDA at any time after the final rule on CGMPs for PET facilities is published. This request is not a part of the drug application process and will probably be handled by the Office of Compliance. It is expected that such requests will be consistent with the PET center's application

submission.

*Q25: If a PET center comprises five hospitals, and we want to manufacture the FDG at one site and distribute it among our five hospitals, are we considered five different manufacturing sites, or is it just distribution among our own departments?*

A: This would be considered one manufacturing site.

*Q26: The PET activities we are doing fall into the category of physiological research. Do we need a CGMP license? Is there a distinction between registration and applications for CGMP?*

A: There are no CGMP licenses or applications. Generally, PET activities require either an IND, NDA, or ANDA (see *Federal Register* notice from February 27, 1995). Activities conducted under any of these applications must be conducted in compliance with applicable CGMP regulations (21 CFR Parts 210 and 211) to ensure product quality for any drug administered to patients.

*Q27: If we were to apply for a limited IND, would that automatically put us into this CGMP process?*

A: Any facility that manufactures drugs for human use should be using CGMPs. The FDA Guideline on the Preparation of Investigational New Drug Products (Human and Animal) dated March 1991 provides guidance on CGMP requirements for investigational new drug (IND) applications.

*Q28: In the guidelines there are three classes of sterile areas. Are there any specific space requirements for each of these particular areas?*

A: No. There should be adequately defined space to prevent contamination or mixups to do the job effectively, as described in 21 CFR 211.42.

*Q29: Is there a mechanism by which some of you could come and spend some significant amount of time in one or more PET centers and actually see and really understand how we have to work?*

A: Yes. Send a letter to the Director, Office of Compliance, HFD-300, 7520 Standish Place, Rockville, Maryland 20855, requesting a visit.

*Q30: Is it possible for you to simplify the ANDA process, at least for FDG manufacturing? Can you provide some addresses for applying for ANDAs?*

A: We intend to do everything we can to simplify the regulatory processes. The staffs in the Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD)

and Office of Compliance (OC) will be available to help answer questions whenever needed during the application process. All application packages (IND, NDA and ANDA) can be obtained by calling the CDER Drug Information Branch at 301-827-4573. The application contains the mailing addresses for the different Offices.

*Q31: How do we handle apparent conflicts between CGMP and Nuclear Regulatory Commission (NRC) regulations with respect to sterile product preparation? The FDA likes to have everything under positive pressure, hepa-filtered coming in. NRC likes to have everything under negative pressure, hepa-filtered going out. How can this conflict be resolved?*

A: The section on environmental controls in the draft guidance has been written to address CGMP requirements, and there are ways to proceed according to the guidance that would not conflict with negative pressure requirements. At this time, the FDA is unaware of any other conflicts.

*Q32: If an academic institution is registered as a manufacturer and has an approved NDA for a PET radiopharmaceutical, are we free to market and distribute this drug anywhere?*

A: Yes, as long as the applicable requirements of the FD&C Act and other Federal laws have been met.

*Q33: It seems that the guidelines were written for FDG and then in a few places it says they're applicable to other PET radiopharmaceuticals. We make more radioactive water drug products than any other place, and we are talking about doing the clinical use. If I look at how we make O-15 water, we'd have to ask for an alternative or an exception for virtually every step of the process. Does that mean you would be expecting 20 or 30 different requests for alternatives or exceptions where we have to deviate because these were written for something with a 108 minute half-life?*

A: What you are describing was never under consideration in the preparation of the draft guideline. The guideline was written with liquid injectable PET products in mind, using F-18 FDG as an example. Every request for an exception or an alternative should be documented and justified. However, a number of requests can be bundled together in one application.

*Q34: If a PET NDA holder contracts with another PET facility to manufacture a PET radiopharmaceutical, is the NDA holder liable for CGMP violations of the contract manufacture?*

A: NDA holders (sponsors) are responsible for meeting all application commitments and for ensuring that contract facilities comply with all applicable provisions of the FD&C Act (Act) and regulations. Because the contract manufacturer is engaged in the

manufacture of a drug, it is also responsible for compliance with the Act and regulations. Decisions to initiate FDA enforcement actions are made based on the facts of each particular case.

*Q35: If a PET IND holder distributes a PET radiopharmaceutical to another PET facility that fails to comply with the IND regulations (commercial distribution of an investigational new drug), who is liable?*

A: IND holders (sponsors) are responsible for, among other things, selecting qualified investigators, ensuring proper monitoring of the investigations and ensuring that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND (see 21 CFR § 312.50).

More specifically, under 21 CFR § 312.56(b), a sponsor who discovers that an investigator is not complying with the signed agreement, the general investigational plan, or the requirements of 21 CFR Part 312 or other applicable regulations, must promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. Investigators are also responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and for the control of drugs under investigation (see 21 CFR § 312.60, 312.61). Decisions to initiate FDA enforcement actions are made based on the facts of each particular case.

*Q36: Must ANDA applicants obtain a letter of authorization from ICP for their chemistry DMF, or is the NDA complete as submitted to support the review of an ANDA for F-18 FDG?*

A: A Drug Master File (DMF) is a mechanism by which a company can supply information to FDA for review without having to directly give the information to IND or NDA/ANDA applicants. The DMF is maintained at the agency and FDA reviewers can look at the data in the DMF, but the data are not shared with anyone outside of the agency. DMF's provide a mechanism to protect proprietary information. If an applicant wants to use data in a DMF that they do not own, a letter of authorization from the DMF holder must be provided to the applicant and must be submitted with the application to allow FDA access to the DMF data while reviewing the application. A letter of authorization does not give the applicant permission to see the DMF. An ANDA applicant does not need a letter of authorization from the innovator drug sponsor in order to submit an ANDA.

An ANDA applicant has several options when preparing an application for submission. The applicant may:

- Generate and submit all of their own data and information

- Collect and analyze published literature that may supply the needed information.

- Acquire a letter of authorization from the DMF holder if the information provided in the DMF contains data essential to the review and approval for the ANDA.

- Acquire a letter of authorization from another applicant who may have the data in their application.

For example, if a DMF contained information on a particular cyclotron or chemical processing unit that was not available from another source, an ANDA applicant proposing to use that cyclotron and chemical processing unit could obtain a letter of authorization from the DMF holder to reference the DMF. Using information in a DMF may save time and effort of the part of the applicant, but is not required if the information is available from another source.